

Article

New Isoxazolidine-Conjugates of Quinazolinones—Synthesis, Antiviral and Cytostatic Activity

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Abstract: A novel series of (3-diethoxyphosphoryl)isoxazolidines substituted at C5 with various quinazolinones have been synthesized by the 1,3-dipolar cycloaddition of *N*-methyl-*C*-(diethoxyphosphoryl)nitron with *N*3-substituted 2-vinyl-3*H*-quinazolin-4-ones. All isoxazolidines were assessed for antiviral activity against a broad range of DNA and RNA viruses. Isoxazolidines *trans*-**11f**/*cis*-**11f** (90:10), *trans*-**11h** and *trans*-**11i**/*cis*-**11i** (97:3) showed weak activity (EC_{50} = 6.84, 15.29 and 9.44 μ M) toward VZV (TK⁺ strain) which was only one order of magnitude lower than that of acyclovir used as a reference drug. Phosphonates *trans*-**11b**/*cis*-**11b** (90:10), *trans*-**11c**, *trans*-**11e**/*cis*-**11e** (90:10) and *trans*-**11g** appeared slightly active toward cytomegalovirus (EC_{50} = 27–45 μ M). Compounds containing benzyl substituents at N3 in the quinazolinone skeleton exhibited slight antiproliferative activity towards the tested immortalized cells with IC_{50} in the 21–102 μ M range.

Keywords: phosphonate; isoxazolidine; quinazolinones; antiviral; cytostatic

1. Introduction

Nitrogen-containing heterocycles form the core of natural products (e.g., alkaloids) and they are also present in many pharmacophores as well as in numerous marketed drugs. Among them, quinazolines and quinazolinones have drawn special attention due to the broad spectrum of biological activities of their derivatives, including sedative [1–3], anticancer [4–7], antiviral [8–12], antibacterial [13–15], antifungal [15,16], anti-inflammatory [15,17–19] and antifibrotic [20,21] activities. Several reviews focused on the synthetic strategies and biological activities of these compounds have been published [22–29]. The significant impact of various functional groups installed into quinazoline/quinazolinone frameworks on pharmacological properties have been proven.

In the last decades several compounds containing the quinazolin-4-one framework, which exhibited promising anticancer as well as antiviral properties, have been obtained (Figure 1). Furthermore, some biologically active substituted quinazolin-4(3*H*)-ones were isolated from various fungi and bacteria species. For example, 2-(4-hydroxybenzyl)quinazolin-4(3*H*)-one (**1**) was found in an entomopathogenic fungus *Isaria farinosa* and its strong inhibitory properties on the replication of tobacco mosaic virus (TMV) [30] were recognised, whereas its 2-(4-hydroxybenzoyl) analogue **2** present in fungus from *Penicillium* genus appeared only slightly active toward TMV [30]. Moreover, compound **1** exhibited significant cytotoxicity toward various cancer cell lines [31,32].

Quinazolinone **3** isolated from *Streptomyces* sp. appeared cytotoxic against Vero cells [33]. Very recently synthetic pyridine-containing analogue **4** and its 3-substituted derivatives **5** and **6** have been obtained and their slight activity against influenza A virus was revealed [34]. On the other hand, various 2,3-disubstituted quinazolin-4(3H)-ones, including compounds **7–10**, have been found to possess antitumor activity [35].

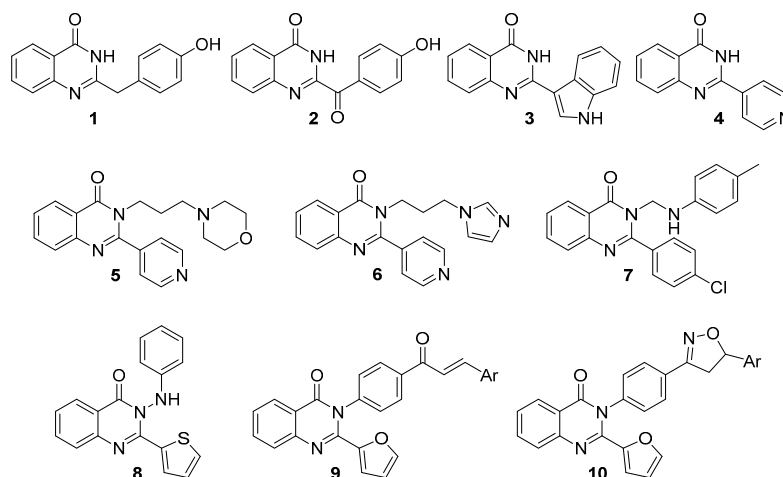
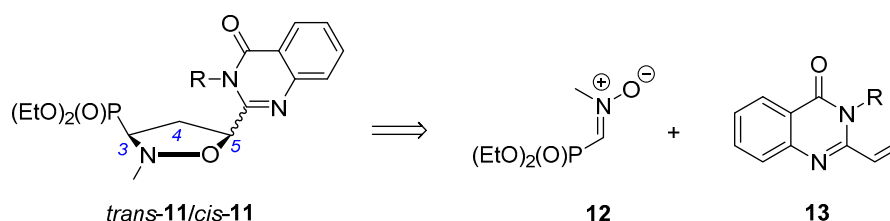


Figure 1. Examples of quinazolinones with antiviral and anticancer activity.

In continuation of our studies on antiviral and cytostatic activity of isoxazolidine analogues of C-nucleoside analogues, we designed a new series of compounds of the general formula **11** containing a substituted quinazolinone moiety as a false nucleobase at C5 in the isoxazolidine ring and the diethoxyphosphoryl function attached at C3. Our synthetic strategy to compounds *trans*-**11**/*cis*-**11** relies on the 1,3-dipolar cycloaddition of *N*-methyl-C-(diethoxyphosphoryl)nitron **12** [36] with 2-vinyl-3H-quinazolin-4-ones **13** substituted at N3 (Scheme 1).

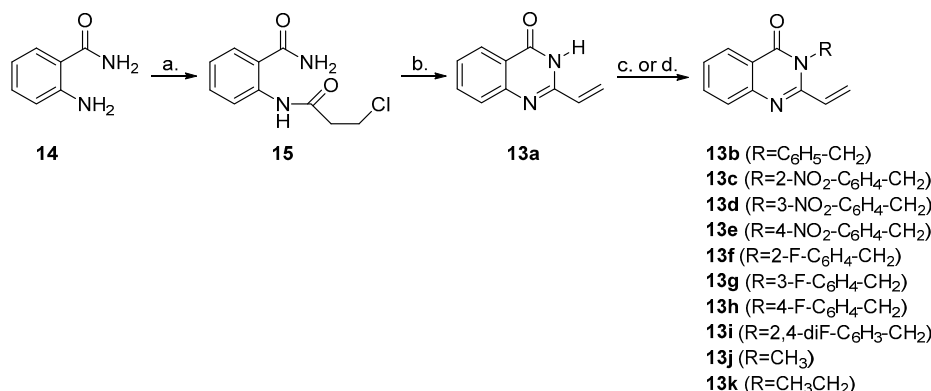


Scheme 1. Retrosynthesis of (isoxazolidinyl) phosphonates *trans*-**11**/*cis*-**11**.

2. Results and Discussion

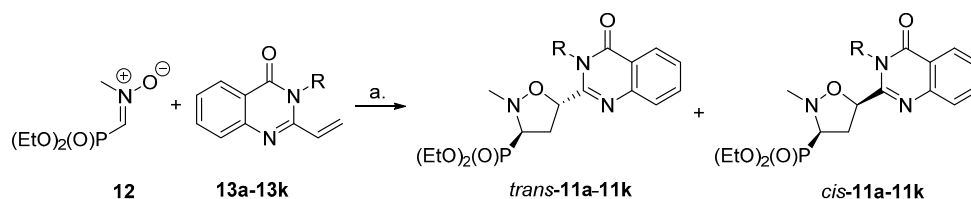
2.1. Chemistry

2-Vinyl-3H-quinazolin-4-ones **13** modified at N3 with substituted benzyl groups were synthesized from commercially available 2-aminobenzamide (**14**) by acylation with 3-chloro-propionyl chloride followed by cyclization and dehydrohalogenation to prepare 2-vinyl-3H-quinazolin-4-one (**13a**) as a key intermediate [37] and a subsequent reaction with substituted benzyl bromides **13b–i** [38] (Scheme 2). Moreover, compounds **13j** (R = Me) and **13k** (R = Et) were also obtained with intention to determine the influence of the benzyl substituent on biological activity of the designed isoxazolidines *trans*-**11**/*cis*-**11**. In the ¹H-NMR spectra of compounds **13a–k** characteristic signals for vinyl protons were observed in the 6.94–5.59 ppm (three doublets of doublets).



Scheme 2. Synthesis of Compounds **13a–k**. *Reaction and conditions:* a. 3-chloropropionyl chloride, 1,4-dioxane, 0 °C; b. 5% NaOH-EtOH (2:1); c. RBr, KOH, CH₃CN, 105 °C; d. MeI or EtI, KOH, CH₃CN, 60 °C.

The 1,3-dipolar cycloaddition of a nitron **12** with 2-vinylquinazolinones **13a–k** led to the formation of diastereoisomeric mixtures of 5-substituted (3-diethoxyphosphoryl)isoxazolidines *trans*-**11** and *cis*-**11** with good (80%–88%) diastereoselectivities (Scheme 3, Table 1). Ratios of *cis/trans* diastereoisomers were calculated from ³¹P-NMR spectra of crude reaction mixtures and confirmed by the analysis of ¹H-NMR spectral data. Crude mixtures of isoxazolidine cycloadducts were then subjected to purification on silica gel columns. However, attempts to isolate pure diastereoisomers were fruitful for *trans*-**11a** (R = H), *trans*-**11c** (R = 2-NO₂-C₆H₄-CH₂), *trans*-**11g** (R = 3-F-C₆H₄-CH₂), *trans*-**11h** (R = 4-F-C₆H₄-CH₂) and *trans*-**11j** (R = Me) only.



Scheme 3. Synthesis of Isoxazolidines *cis*-**11a–k** and *trans*-**11a–k**. *Reaction and conditions:* a. toluene, 70 °C, 24 h.

Table 1. Isoxazolidines *trans*-**11** and *cis*-**11** obtained according to Scheme 3.

Entry	Quinazolinone 13 R	Ratio of <i>Trans</i> -11: <i>Cis</i> -11	Yield (%)
a	H	92:8	<i>trans</i> - 11a (23) ^a + <i>trans</i> - 11a and <i>cis</i> - 11a (70) ^b
b	C ₆ H ₅ -CH ₂	90:10	<i>trans</i> - 11b and <i>cis</i> - 11b (84) ^b
c	2-NO ₂ -C ₆ H ₄ -CH ₂	90:10	<i>trans</i> - 11c (20) ^a + <i>trans</i> - 11c and <i>cis</i> - 11c (73) ^b
d	3-NO ₂ -C ₆ H ₄ -CH ₂	92:8	<i>trans</i> - 11d and <i>cis</i> - 11d (98) ^b
e	4-NO ₂ -C ₆ H ₄ -CH ₂	90:10	<i>trans</i> - 11e and <i>cis</i> - 11e (91) ^b
f	2-F-C ₆ H ₄ -CH ₂	90:10	<i>trans</i> - 11f and <i>cis</i> - 11f (94) ^b
g	3-F-C ₆ H ₄ -CH ₂	90:10	<i>trans</i> - 11g (7) ^a + <i>trans</i> - 11g and <i>cis</i> - 11g (89) ^b
h	4-F-C ₆ H ₄ -CH ₂	90:10	<i>trans</i> - 11h (22) ^a + <i>trans</i> - 11h and <i>cis</i> - 11h (70) ^b
i	2,4-diF-C ₆ H ₃ -CH ₂	92:8	<i>trans</i> - 11i and <i>cis</i> - 11i (94) ^b
j	Me	94:6	<i>trans</i> - 11j (19) ^a + <i>trans</i> - 11j and <i>cis</i> - 11j (78) ^b
k	Et	92:8	<i>trans</i> - 11k and <i>cis</i> - 11k (86) ^b

^a yield of pure isomer; ^b yield of pure mixture of *cis*- and *trans*-isomers.

The relative configurations of isoxazolidines *trans*-**11a** and *cis*-**11a** were established based on our previous studies on stereochemistry of cycloaddition of *N*-methyl-C-(diethoxyphosphoryl)nitron (**12**)

with various vinyl aryls [39,40] since similar ^1H -NMR spectral patterns for the respective series of *trans*- and *cis*-isoxazolidines were observed. Since for compound *trans*-11a all necessary coupling constants were successfully extracted from the ^1H - and ^{13}C -NMR spectra, detailed conformational analysis was performed based on these data [$J_{(\text{H}3-\text{H}4\alpha)} = 9.3 \text{ Hz}$ [41], $J_{(\text{H}3-\text{H}4\beta)} = 8.3 \text{ Hz}$, $J_{(\text{H}4\alpha-\text{P})} = 9.9 \text{ Hz}$ [42,43], $J_{(\text{H}4\beta-\text{P})} = 16.9 \text{ Hz}$, $J_{(\text{H}4\alpha-\text{H}5)} = 6.2 \text{ Hz}$, $J_{(\text{H}4\beta-\text{H}5)} = 8.3 \text{ Hz}$, $J_{(\text{CCCCP})} = 8.5 \text{ Hz}$ [44,45]] and revealed that isoxazolidine ring in *trans*-11a adopts a 3E conformation in which the diethoxyphosphoryl group resides in the equatorial position of the isoxazolidine ring while a quinazolinone substituent is located pseudoequatorially (Figure 2). On the other hand, *cis* configuration of the minor isomer was established from the corresponding couplings [$J_{(\text{H}3-\text{H}4\alpha)} = 9.0 \text{ Hz}$, $J_{(\text{H}3-\text{H}4\beta)} = 6.5 \text{ Hz}$, $J_{(\text{H}4\alpha-\text{P})} = 11.2 \text{ Hz}$, $J_{(\text{H}4\beta-\text{P})} = 20.0 \text{ Hz}$, $J_{(\text{H}4\alpha-\text{H}5)} = 9.1 \text{ Hz}$, $J_{(\text{H}4\beta-\text{H}5)} = 3.9 \text{ Hz}$, $J_{(\text{CCCCP})} = 7.3 \text{ Hz}$] indicating the 2E conformation of the isoxazolidine ring (Figure 2). The additional arguments to support our assignments follow from shielding of the $\text{CH}_3\text{CH}_2\text{OP}$ protons observed for the *cis* isomer ($\Delta\delta$ ca. 0.1 ppm) when compared with the *trans*-11a. Furthermore, it was found that on a ^1H -NMR spectrum taken on the 83:17 mixture of *cis*- and *trans*-11a, the H-N proton in the quinazolinone ring of *cis*-11a was significantly deshielded ($\Delta\delta = 0.7 \text{ ppm}$) when compared with the *trans* isomer, highly likely, as a result of the hydrogen bond formation with the phosphoryl oxygen amide, a phenomenon spatially achievable in the *cis* isomer only.

Since introduction of various substituents at N3 of quinazolinone moiety has no influence on the stereochemical outcome of the cycloaddition therefore configuration of the all major isoxazolidines 11 were assigned as *trans*, thereby minor ones as *cis*.

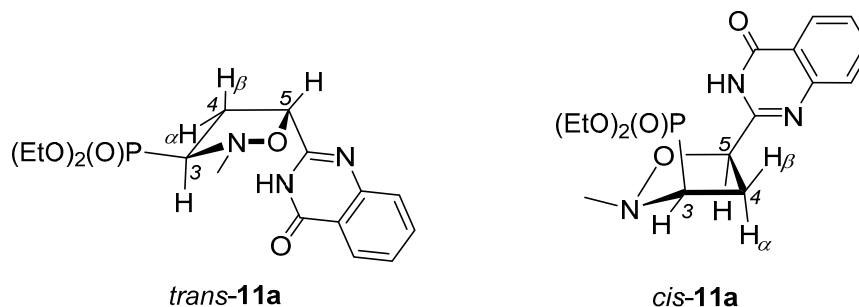


Figure 2. The preferred conformations of *trans*-isoxazolidine *trans*-11a.

2.2. Antiviral and Cytostatic Evaluation

2.2.1. Antiviral Activity

All obtained phosphonates *trans*-11a, *trans*-11c, *trans*-11g, *trans*-11h and *trans*-11j as well as mixtures of diastereoisomeric phosphonates *trans*-11b/*cis*-11b (90:10), *trans*-11d/*cis*-11d (90:10), *trans*-11e/*cis*-11e (90:10), *trans*-11f/*cis*-11f (90:10), *trans*-11i/*cis*-11i (97:3) and *trans*-11k/*cis*-11k (97:3) were evaluated for inhibitory activity against a wide variety of DNA and RNA viruses, using the following cell-based assays: (a) human embryonic lung (HEL) cells: herpes simplex virus-1 (KOS), herpes simplex virus-2 (G), thymidine kinase deficient (acyclovir resistant) herpes simplex virus-1 (TK[−] KOS ACV⁺), vaccinia virus, adeno virus-2, vesicular stomatitis virus, cytomegalovirus (AD-169 strain -1 and Davis strain), varicella-zoster virus (TK⁺ VZV Oka strain and TK[−] VZV 07-1 strain); (b) HeLa cell cultures: vesicular stomatitis virus, Coxsackie virus B4 and respiratory syncytial virus; (c) Vero cell cultures: para-influenza-3 virus, reovirus-1, Sindbis virus, Coxsackie virus B4, Punta Toro virus, yellow fever virus; (e) CRFK cell cultures: feline corona virus (FIPV) and feline herpes virus (FHV) and (d) MDCK cell cultures: influenza A virus (H1N1 and H3N2 subtypes) and influenza B virus. Ganciclovir, cidofovir, acyclovir, brivudin, zalcitabine, zanamivir, alovudine, amantadine, rimantadine, ribavirin, dextran sulfate (molecular weight 10,000, DS-10000), mycophenolic acid, Hipppeastrum hybrid agglutinin (HHA) and *Urtica dioica* agglutinin (UDA) were used as the reference compounds.

The antiviral activity was expressed as the EC₅₀: the compound concentration required to reduce virus plaque formation (VZV) by 50% or to reduce virus-induced cytopathogenicity by 50% (other viruses).

Several isoxazolidines *trans*-**11**/*cis*-**11** were able to weakly inhibit the replication of TK⁺ and TK[−] VZV strains with EC₅₀ values in the range of 6.84–100 µM (Table 2). Among them, phosphonates *trans*-**11f**/*cis*-**11f** (90:10) (R = 2-F-C₆H₄-CH₂) (EC₅₀ = 6.84 µM), *trans*-**11h** (R = 4-F-C₆H₄-CH₂) (EC₅₀ = 15.29 µM), *trans*-**11i**/*cis*-**11i** (97:3) (R = 2,4-diF-C₆H₃-CH₂) (EC₅₀ = 9.44 µM) were the most active toward TK⁺ VZV Oka strain, while exhibiting no activity toward TK[−] VZV strain. The activity of these isoxazolidines *trans*-**11**/*cis*-**11** against TK⁺ VZV Oka strain was 8- to 22-folds lower than that of the reference drug acyclovir.

Table 2. Cytotoxicity and antiviral activity against varicella-zoster virus (VZV) in HEL cell cultures.

Compound	R	Antiviral Activity EC ₅₀ (µM) ^a		Cytotoxicity (µM)
		TK ⁺ VZV Strain	TK [−] VZV Strain	Cell Morphology MCC ^b
<i>trans</i> - 11c	2-NO ₂ -C ₆ H ₄ -CH ₂	46.47	100	>100
<i>trans</i> - 11e / <i>cis</i> - 11e (90:10)	4-NO ₂ -C ₆ H ₄ -CH ₂	34.20	42.87	100
<i>trans</i> - 11f / <i>cis</i> - 11f (90:10)	2-F-C ₆ H ₄ -CH ₂	6.84	>20	100
<i>trans</i> - 11h	4-F-C ₆ H ₄ -CH ₂	15.29	>20	100
<i>trans</i> - 11i / <i>cis</i> - 11i (97:3)	2,4-diF-C ₆ H ₃ -CH ₂	9.44	>20	100
<i>trans</i> - 11k	CH ₃ CH ₂	38.80	41.57	>100
Acyclovir		0.71	39.69	>100
Brivudin		0.019	25.59	>100

^a Effective concentration required to reduce virus plaque formation by 50%. Virus input was 100 plaque forming units (PFU); ^b Minimum cytotoxic concentration that causes a microscopically detectable alternation of cell morphology.

On the other hand, the EC₅₀ values for the TK[−] VZV 07-1 strain (which is an acyclovir resistant strain) of the phosphonates *trans*-**11e**/*cis*-**11e** (90:10) (R = 4-NO₂-C₆H₄-CH₂) (EC₅₀ = 42.87 µM) and *trans*-**11k**/*cis*-**11k** (97:3) (R = Et) (EC₅₀ = 41.57 µM) were comparable to that of acyclovir (EC₅₀ = 39.69 µM). These derivatives showed similar EC₅₀'s for TK⁺ and TK[−] VZV strains and therefore their potency against TK⁺ VZV was approximately 50-fold lower compared to acyclovir.

Furthermore, compounds *trans*-**11b**/*cis*-**11b** (90:10) (R = C₆H₅-CH₂), *trans*-**11c** (R = 2-NO₂-C₆H₄-CH₂), *trans*-**11e**/*cis*-**11e** (90:10) (R = 4-NO₂-C₆H₄-CH₂) and *trans*-**11g** (R = 3-F-C₆H₄-CH₂) showed some activity against human cytomegalovirus (EC₅₀ = 27–45 µM), although they were less active than ganciclovir and cidofovir used as the reference compounds (Table 3). None of the phosphonate derivatives here described showed activity against the other tested DNA and RNA viruses.

Table 3. Antiviral activity and cytotoxicity against human cytomegalovirus in HEL cell cultures.

Compound	R	Antiviral Activity EC ₅₀ (µM) ^a		Cytotoxicity (µM)
		AD-169 Strain	Davis Strain	Cell Morphology MCC ^b
<i>trans</i> - 11b / <i>cis</i> - 11b (90:10)	C ₆ H ₅ -CH ₂	44.72	>20	≥100
<i>trans</i> - 11c	2-NO ₂ -C ₆ H ₄ -CH ₂	>100	44.72	≥20
<i>trans</i> - 11e / <i>cis</i> - 11e (90:10)	4-NO ₂ -C ₆ H ₄ -CH ₂	44.72	20	>100
<i>trans</i> - 11g	3-F-C ₆ H ₄ -CH ₂	>100	27.59	100
Ganciclovir		10.52	0.63	>350
Cidofovir		1.49	0.23	>300

^a Effective concentration required to reduce virus plaque formation by 50%. Virus input was 100 plaque forming units (PFU); ^b Minimum cytotoxic concentration that causes a microscopically detectable alternation of cell morphology.

2.2.2. Cytostatic Activity

The 50% cytostatic inhibitory concentration (IC₅₀) causing a 50% decrease in cell proliferation was determined against murine leukemia L1210, human lymphocyte CEM, human cervix carcinoma HeLa and immortalized human dermal microvascular endothelial cells (HMEC-1). Isoxazolidines *trans*-**11a** (R = H) and *trans*-**11j** (R = Me) did not inhibit cell proliferation at the highest tested concentration

(i.e., 250 μM), whereas *trans*-**11k**/*cis*-**11k** (97:3) ($R = \text{Et}$) appeared slightly cytostatic towards the tested cell lines ($\text{IC}_{50} = 85\text{--}101 \mu\text{M}$). On the other hand (Table 4, entries **b** to **i**), compounds having benzyl substituents at N3 in the quinazolinone moiety showed lower IC_{50} values ($\text{IC}_{50} = 21\text{--}102 \mu\text{M}$) thereby indicating that installation of functionalized benzyl groups was profitable for inhibitory properties.

Table 4. Inhibitory effect of the tested compounds against the proliferation of murine leukemia (L1210), human T-lymphocyte (CEM), human cervix carcinoma (HeLa) and immortalized human dermal microvascular endothelial cells (HMEC-1).

Compound	R	IC_{50}^a (μM)			
		L1210	CEM	HeLa	HMEC-1
<i>trans</i> - 11a	H	>250	>250	>250	>250
<i>trans</i> - 11b / <i>cis</i> - 11b (90:10)	$\text{C}_6\text{H}_5\text{-CH}_2$	49 ± 23	28 ± 4	82 ± 5	83 ± 16
<i>trans</i> - 11c	$2\text{-NO}_2\text{-C}_6\text{H}_4\text{-CH}_2$	87 ± 22	76 ± 9	97 ± 0	92 ± 1
<i>trans</i> - 11d / <i>cis</i> - 11d (90:10)	$3\text{-NO}_2\text{-C}_6\text{H}_4\text{-CH}_2$	28 ± 11	21 ± 4	50 ± 4	58 ± 0
<i>trans</i> - 11e / <i>cis</i> - 11e (90:10)	$4\text{-NO}_2\text{-C}_6\text{H}_4\text{-CH}_2$	59 ± 32	34 ± 12	76 ± 4	102 ± 3
<i>trans</i> - 11f / <i>cis</i> - 11f (90:10)	$2\text{-F-C}_6\text{H}_4\text{-CH}_2$	33 ± 7	29 ± 13	76 ± 11	77 ± 0
<i>trans</i> - 11g	$3\text{-F-C}_6\text{H}_4\text{-CH}_2$	35 ± 12	26 ± 6	62 ± 9	74 ± 3
<i>trans</i> - 11h	$4\text{-F-C}_6\text{H}_4\text{-CH}_2$	26 ± 1	30 ± 12	58 ± 5	78 ± 1
<i>trans</i> - 11i / <i>cis</i> - 11i (97:3)	$2,4\text{-diF-C}_6\text{H}_3\text{-CH}_2$	26 ± 2	24 ± 8	55 ± 10	67 ± 4
<i>trans</i> - 11j	Me	>250	>250	>250	>250
<i>trans</i> - 11k / <i>cis</i> - 11k (97:3)	Et	101 ± 17	85 ± 13	97 ± 10	86 ± 11
5-Fluorouracil		0.33 ± 0.17	18 ± 5	0.54 ± 0.12	n.d.

^a 50% Inhibitory concentration or compound concentration required to inhibit tumor cell proliferation by 50%; n.d.—not determined.

3. Experimental Section

3.1. General

^1H -NMR spectra were taken in CDCl_3 on the following spectrometers: Gemini 2000BB (200 MHz Varian, Palo Alto, CA, USA), and Avance III (600 MHz, Bruker Instruments, Karlsruhe, Germany) with TMS as internal standard. ^{13}C -NMR spectra were recorded for CDCl_3 solution on the Bruker Avance III at 151.0 MHz. ^{31}P -NMR spectra were performed in CDCl_3 solution on the Varian Gemini 2000 BB at 81.0 MHz or on Bruker Avance III at 243.0 MHz. IR spectra were measured on an Infinity MI-60 FT-IR spectrometer (ATI Instruments North America-Mattson, Madison, WI, USA). Melting points were determined on a Boetius apparatus (VEB Kombinat NAGEMA, Dresden, Germany) and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of this Faculty on Perkin-Elmer PE 2400 CHNS analyzer (Perkin-Elmer Corp., Norwalk, CT, USA). The following adsorbents were used: column chromatography, Merck silica gel 60 (70–230 mesh); analytical TLC, Merck (Merck KGaA, Darmstadt, Germany) TLC plastic sheets silica gel 60 F₂₅₄. *N*-methyl-*C*-(diethoxyphosphoryl)nitron (12) [36], 2-vinyl-3*H*-quinazolin-4-one (13a) [37] and 3-methyl-2-vinyl-3*H*-quinazolin-4-one (13j) [38] were obtained according to the literature procedures.

^1H -, ^{13}C - and ^{31}P -NMR spectra of all new synthesised compounds are provided in Supplementary Materials (Figures S1–S54).

3.2. General Procedure for the Synthesis of *N*3-Benzylated 2-Vinyl-3*H*-quinazolin-4-ones 13b–i

To the solution of 2-vinyl-3*H*-quinazolin-4-one (13a, 1.00 mmol) in acetonitrile (15 mL) potassium carbonate (3.00 mmol) was added. After 15 min the respective benzyl bromide (1.10 mmol) was added and the reaction mixture was stirred under reflux for 4 h. A solvent was removed and the residue was extracted with water ($3 \times 10 \text{ mL}$). An organic layer was dried (MgSO_4), concentrated and the crude product was purified on a silica gel column with a methylene chloride: hexane mixture (7:3, *v/v*) followed by crystallisation (chloroform-petroleum ether) to give pure quinazolinones 13b–e and 13g–i.

3-Benzyl-2-vinylquinazolin-4(3H)-one (13b). White amorphous solid, m.p. = 85 °C–87 °C (reference [46]—colorless viscous oil). IR (KBr, cm^{-1}) ν_{max} : 3027, 2950, 2925, 1677, 1615, 1574, 1425, 1312, 1271, 952, 845, 778, 755, 585. ^1H -NMR (200 MHz, CDCl_3): δ = 8.20–8.19 (m, 1H), 7.92–7.88 (m, 1H), 7.83–7.78 (m, 1H), 7.58–7.49 (m, 3H), 7.46–7.36 (m, 3H), 6.94 (dd, 3J = 17.2 Hz, 3J = 10.1 Hz, 1H, $\text{CH}=\text{CH}_2$), 6.73 (dd, 3J = 17.2 Hz, 2J = 2.3 Hz, 1H, $\text{CH}=\text{CH}_2$), 5.80 (dd, 3J = 10.1 Hz, 2J = 2.3 Hz, 1H, $\text{CH}=\text{CH}_2$), 5.69 (s, 2H, N- CH_2). ^{13}C -NMR (151 MHz, CDCl_3): δ = 166.12 (s, C(O)), 159.97, 151.63, 137.17, 136.44, 133.57, 128.60, 128.28, 128.25, 127.67, 126.60, 123.81, 123.61, 115.59, 68.32 (s, N- CH_2). Anal. Calcd. for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.69; H, 5.21; N, 10.88.

3-(2-Nitrobenzyl)-2-vinylquinazolin-4(3H)-one (13c). Yellowish amorphous solid, m.p. = 88 °C–91 °C. IR (KBr, cm^{-1}) ν_{max} : 2952, 2851, 1615, 1574, 1525, 1493, 1396, 1312, 988, 1104, 988, 938, 780, 723, 664. ^1H -NMR (600 MHz, CDCl_3): δ = 8.24–8.22 (m, 1H), 8.18–8.16 (m, 1H), 7.96–7.94 (m, 1H), 7.87–7.82 (m, 2H), 7.69–7.67 (m, 1H), 7.59–7.53 (m, 2H), 6.91 (dd, 3J = 17.2 Hz, 3J = 10.4 Hz, 1H, $\text{CH}=\text{CH}_2$), 6.64 (dd, 3J = 17.2 Hz, 2J = 1.2 Hz, 1H, $\text{CH}=\text{CH}_2$), 6.14 (s, 2H, N- CH_2), 5.78 (dd, 3J = 10.4 Hz, 2J = 1.2 Hz, 1H, $\text{CH}=\text{CH}_2$). ^{13}C -NMR (151 MHz, CDCl_3): δ = 165.51 (s, C(O)), 159.83, 151.80, 147.86, 136.77, 133.78, 133.65, 132.77, 129.02, 128.67, 128.86, 127.86, 126.85, 124.97, 124.12, 123.56, 123.26, 115.26, 64.79 (s, N- CH_2). Anal. Calcd. for $\text{C}_{17}\text{H}_{13}\text{N}_3\text{O}_3$: C, 66.44; H, 4.26; N, 13.67. Found: C, 66.23; H, 4.11; N, 13.38.

3-(3-Nitrobenzyl)-2-vinylquinazolin-4(3H)-one (13d). Yellowish amorphous solid, m.p. = 90 °C–93 °C. IR (KBr, cm^{-1}) ν_{max} : 3093, 3020, 2958, 2941, 1615, 1574, 1562, 1523, 1345, 1044, 991, 965, 801, 764, 687. ^1H -NMR (600 MHz, CDCl_3): δ = 8.46 (brs, 1H), 8.25–8.23 (m, 1H), 8.22–8.20 (m, 1H), 7.94–7.89 (m, 2H), 7.86–7.83 (m, 1H), 7.63–7.60 (m, 1H), 7.57–7.55 (m, 1H), 6.94 (dd, 3J = 17.2 Hz, 3J = 10.4 Hz, 1H, $\text{CH}=\text{CH}_2$), 6.71 (dd, 3J = 17.2 Hz, 2J = 1.6 Hz, 1H, $\text{CH}=\text{CH}_2$), 5.82 (dd, 3J = 10.4 Hz, 2J = 1.6 Hz, 1H, $\text{CH}=\text{CH}_2$), 5.80 (s, 2H, N- CH_2). ^{13}C -NMR (151 MHz, CDCl_3): δ = 165.61 (s, C(O)), 159.72, 151.74, 148.48, 138.58, 136.98, 133.89, 133.82, 129.61, 127.82, 126.88, 123.89, 123.33, 123.15, 122.98, 115.24, 66.83 (s, N- CH_2). Anal. Calcd. for $\text{C}_{17}\text{H}_{13}\text{N}_3\text{O}_3$: C, 66.44; H, 4.26; N, 13.67. Found: C, 66.12; H, 3.97; N, 13.40.

3-(4-Nitrobenzyl)-2-vinylquinazolin-4(3H)-one (13e). Yellowish amorphous solid, m.p. = 131 °C–132 °C. IR (KBr, cm^{-1}) ν_{max} : 2944, 2849, 1608, 1570, 1514, 1488, 1338, 1162, 984, 854, 812, 704, 680. ^1H -NMR (600 MHz, CDCl_3): δ = 8.30–8.28 (m, 2H), 8.24–8.21 (m, 1H), 7.96–7.94 (m, 1H), 7.87–7.84 (m, 1H), 7.73–7.72 (m, 2H), 7.58–7.55 (m, 1H), 6.93 (dd, 3J = 17.2 Hz, 3J = 10.4 Hz, 1H, $\text{CH}=\text{CH}_2$), 6.68 (dd, 3J = 17.2 Hz, 2J = 1.8 Hz, 1H, $\text{CH}=\text{CH}_2$), 5.82 (s, 2H, N- CH_2), 5.80 (dd, 3J = 10.4 Hz, 2J = 1.6 Hz, 1H, $\text{CH}=\text{CH}_2$). ^{13}C -NMR (151 MHz, CDCl_3): δ = 165.59 (s, C(O)), 159.74, 151.78, 147.77, 143.81, 136.97, 133.87, 128.31, 127.89, 126.91, 123.91, 123.85, 123.27, 115.25, 66.78 (s, N- CH_2). Anal. Calcd. for $\text{C}_{17}\text{H}_{13}\text{N}_3\text{O}_3$: C, 66.44; H, 4.26; N, 13.67. Found: C, 66.23; H, 4.03; N, 13.33.

3-(2-Fluorobenzyl)-2-vinylquinazolin-4(3H)-one (13f). Colorless oil; IR (film, cm^{-1}) ν_{max} : 3061, 1676, 1618, 1496, 1422, 1349, 1104, 988, 941, 759, 680, 661. ^1H -NMR (200 MHz, CDCl_3): δ = 8.17–8.13 (m, 1H), 7.92–7.74 (m, 2H), 7.61–7.45 (m, 2H), 7.41–7.29 (m, 1H), 7.26–7.08 (m, 2H), 6.93 (dd, 3J = 17.2 Hz, 3J = 10.0 Hz, 1H, $\text{CH}=\text{CH}_2$), 6.74 (dd, 3J = 17.2 Hz, 2J = 2.4 Hz, 1H, $\text{CH}=\text{CH}_2$), 5.79 (dd, 3J = 10.0 Hz, 2J = 2.4 Hz, 1H, $\text{CH}=\text{CH}_2$), 5.76 (s, 2H, N- CH_2). ^{13}C -NMR (151 MHz, CDCl_3): δ = 165.95 (s, C(O)), 161.15 (d, $^1J_{\text{CF}}$ = 249.1 Hz, C2), 159.93, 151.69, 137.12, 133.57, 130.54 (d, $^3J_{\text{CCCCF}}$ = 3.5 Hz, C4), 130.13 (d, $^3J_{\text{CCCCF}}$ = 8.5 Hz, C6), 127.71, 126.61, 124.17 (d, $^4J_{\text{CCCCF}}$ = 3.4 Hz, C5), 123.85, 123.66 (d, $^2J_{\text{CCF}}$ = 14.4 Hz, C3), 123.56, 115.54 (d, $^2J_{\text{CCF}}$ = 21.1 Hz, C1), 115.51, 62.16 (d, $^3J_{\text{CCCCF}}$ = 4.4 Hz, N- CH_2). Anal. Calcd. for $\text{C}_{17}\text{H}_{13}\text{FN}_2\text{O}$: C, 72.85; H, 4.67; N, 9.99. Found: C, 72.78; H, 4.41; N, 9.80.

3-(3-Fluorobenzyl)-2-vinylquinazolin-4(3H)-one (13g). White amorphous solid, m.p. = 58 °C–59 °C. IR (KBr, cm^{-1}) ν_{max} : 3095, 3057, 3032, 1618, 1578, 1498, 1422, 1349, 1106, 988, 945, 681, 520. ^1H -NMR (200 MHz, CDCl_3): δ = 8.20–8.15 (m, 1H), 7.93–7.88 (m, 1H), 7.84–7.75 (m, 1H), 7.55–7.47 (m, 1H), 7.39–7.22 (m, 3H), 7.10–7.01 (m, 1H), 6.93 (dd, 3J = 17.2 Hz, 3J = 10.1 Hz, 1H, $\text{CH}=\text{CH}_2$), 6.70 (dd, 3J = 17.2 Hz, 2J = 2.3 Hz, 1H, $\text{CH}=\text{CH}_2$), 5.79 (dd, 3J = 10.1 Hz, 2J = 2.3 Hz, 1H, $\text{CH}=\text{CH}_2$), 5.67 (s, 2H, N- CH_2). ^{13}C -NMR (151 MHz, CDCl_3): δ = 165.88 (s, C(O)), 162.95 (d, $^1J_{\text{CF}}$ = 246.6 Hz, C3), 159.88, 151.69, 138.97 (d, $^3J_{\text{CCCCF}}$ = 7.8 Hz, C5), 137.09, 133.67, 130.15 (d, $^3J_{\text{CCCCF}}$ = 8.8 Hz, C1), 127.75, 126.72,

123.84, 123.53 (d, $^4J_{\text{(CCCCF)}} = 2.4$ Hz, C6), 123.48, 115.45, 115.09 (d, $^2J_{\text{(CCF)}} = 21.0$ Hz, C4), 114.93 (d, $^2J_{\text{(CCF)}} = 22.0$ Hz, C2), 67.39 (s, N-CH₂). Anal. Calcd. for C₁₇H₁₃FN₂O: C, 72.85; H, 4.67; N, 9.99. Found: C, 72.66; H, 4.38; N, 9.95.

3-(4-Fluorobenzyl)-2-vinylquinazolin-4(3H)-one (13h). White amorphous solid, m.p. = 125 °C–127 °C. IR (KBr, cm^{−1}) ν_{max} : 3058, 1677, 1618, 1493, 1425, 1349, 1102, 992, 942, 757, 683, 658. ¹H-NMR (200 MHz, CDCl₃): δ = 8.12–8.07 (m, 1H), 7.87–7.82 (m, 1H), 7.78–7.73 (m, 1H), 7.51–7.40 (m, 3H), 7.10–6.97 (m, 2H), 6.88 (dd, $^3J = 17.2$ Hz, $^3J = 10.1$ Hz, 1H, CH=CH₂), 6.66 (dd, $^3J = 17.2$ Hz, $^2J = 2.3$ Hz, 1H, CH=CH₂), 5.74 (dd, $^3J = 10.1$ Hz, $^2J = 2.3$ Hz, 1H, CH=CH₂), 5.59 (s, 2H, N-CH₂). ¹³C-NMR (151 MHz, CDCl₃): δ = 165.99 (s, C(O)), 162.71 (d, $^1J_{\text{(CF)}} = 249.1$ Hz, C4), 159.90, 151.69, 137.19, 133.59, 132.26 (d, $^4J_{\text{(CCCCF)}} = 3.2$ Hz, C1), 130.22 (d, $^3J_{\text{(CCCCF)}} = 7.7$ Hz, C2, C6), 127.74, 126.62, 123.70, 123.49, 115.55 (d, $^2J_{\text{(CCF)}} = 21.3$ Hz, C3, C5), 67.58 (s, N-CH₂). Anal. Calcd. for C₁₇H₁₃FN₂O: C, 72.85; H, 4.67; N, 9.99. Found: C, 72.67; H, 4.30; N, 9.70.

3-(2,4-Difluorobenzyl)-2-vinylquinazolin-4(3H)-one (13i). Yellowish amorphous solid, m.p. = 67 °C–68 °C. IR (KBr, cm^{−1}) ν_{max} : 3076, 3015, 2929, 1681, 1606, 1574, 1505, 1351, 1279, 1100, 964, 851, 772, 666, 683. ¹H-NMR (200 MHz, CDCl₃): δ = 8.10–8.05 (m, 1H), 7.86–7.82 (m, 1H), 7.78–7.68 (m, 1H), 7.57–7.40 (m, 2H), 6.90–6.78 (m, 2H), 6.88 (dd, $^3J = 17.2$ Hz, $^3J = 10.1$ Hz, 1H, CH=CH₂), 6.67 (dd, $^3J = 17.2$ Hz, $^2J = 2.3$ Hz, 1H, CH=CH₂), 5.74 (dd, $^3J = 10.1$ Hz, $^2J = 2.3$ Hz, 1H, CH=CH₂), 5.65 (s, 2H, N-CH₂). ¹³C-NMR (151 MHz, CDCl₃): δ = 165.84 (s, C(O)), 163.11 (dd, $^1J_{\text{(CF)}} = 249.9$ Hz, $^3J_{\text{(CCCCF)}} = 12.1$ Hz, C2), 161.40 (dd, $^1J_{\text{(CF)}} = 251.2$ Hz, $^3J_{\text{(CCCCF)}} = 12.1$ Hz, C4), 159.85, 151.69, 137.11, 133.64, 131.70 (dd, $^3J_{\text{(CCCCF)}} = 9.8$ Hz, $^3J_{\text{(CCCCF)}} = 5.5$ Hz, C6), 127.75, 126.66, 123.81, 123.46, 119.69 (dd, $^2J_{\text{(CCF)}} = 14.6$ Hz, $^4J_{\text{(CCCCF)}} = 3.6$ Hz, C1), 115.44, 111.40 (dd, $^2J_{\text{(CCF)}} = 21.0$ Hz, $^4J_{\text{(CCCCF)}} = 3.4$ Hz, C5), 104.07 (dd, $^2J_{\text{(CCF)}} = 25.3$ Hz, $^2J_{\text{(CCF)}} = 25.0$ Hz, C3), 61.61 (d, $^3J_{\text{(CCCCF)}} = 4.0$ Hz, N-CH₂). Anal. Calcd. for C₁₇H₁₂F₂N₂O: C, 68.45; H, 4.06; N, 9.39. Found: C, 68.19; H, 3.87; N, 9.45.

3.3. General Procedure for the Synthesis of N3-Alkylated 2-Vinyl-3H-quinazolin-4-ones **13j** and **13k**

To the solution of 2-vinyl-3H-quinazolin-4-one (**13a**, 1.00 mmol) in acetonitrile (15 mL) potassium carbonate (3.00 mmol) was added. After 15 min. iodomethane (2.00 mmol) or iodoethane (1.10 mmol) was added and the reaction mixture was stirred at 60 °C for 5 h. The solvent was removed and a residue was extracted with water (3 × 10 mL). Organic layer was dried (MgSO₄), concentrated and the crude product was purified on a silica gel column with methylene chloride:hexane mixture (7:3, v/v) followed by crystallization (chloroform : petroleum ether) to give pure quinazolinones **13j** [35] or **13k**.

3-Methyl-2-vinylquinazolin-4(3H)-one (13j). Amorphous solid, m.p. = 122 °C–124 °C (reference [35] m.p. = 123 °C–125 °C).

3-Ethyl-2-vinylquinazolin-4(3H)-one (13k). Yellowish oil; IR (film, cm^{−1}) ν_{max} : 3066, 2979, 2927, 2855, 1684, 1621, 1576, 1423, 1381, 1163, 962, 768, 681. ¹H-NMR (200 MHz, CDCl₃): δ = 8.16–8.11 (m, 1H), 7.90–7.85 (m, 1H), 7.81–7.73 (m, 1H), 7.52–7.44 (m, 1H), 6.91 (dd, $^3J = 17.2$ Hz, $^3J = 10.1$ Hz, 1H, CH=CH₂), 6.69 (dd, $^3J = 17.2$ Hz, $^2J = 2.3$ Hz, 1H, CH=CH₂), 5.76 (dd, $^3J = 10.1$ Hz, $^2J = 2.3$ Hz, 1H, CH=CH₂), 4.68 (q, $^3J = 7.1$ Hz, 2H, CH₂CH₃), 1.52 (t, $^3J = 7.1$ Hz, 3H, CH₂CH₃). ¹³C-NMR (151 MHz, CDCl₃): δ = 166.31 (s, C(O)), 160.09, 151.51, 137.29, 133.35, 127.62, 126.39, 123.55, 115.66, 62.70 (s, CH₂CH₃), 14.34 (s, CH₂CH₃). Anal. Calcd. for C₁₂H₁₂N₂O × 0.25 H₂O: C, 70.40; H, 6.15; N, 13.68. Found: C, 70.73; H, 5.92; N, 13.80.

3.4. General Procedure for the Synthesis of Isoxazolidines Trans-**11** and Cis-**11**

A solution of the nitron **12** (1.0 mmol) and the respective vinyl quinazolinone (1.0 mmol) in toluene (2 mL) was stirred at 70 °C until the disappearance (TLC) of the starting nitron. All volatiles were removed *in vacuo* and crude products were subjected to chromatography on silica gel columns with a chloroform/methanol (100:1, 50:1, 20:1, v/v) mixtures as eluents.

Diethyl trans-(2-methyl-5-(4-oxo-3,4-dihydroquinazolin-2-yl)isoxazolidin-3-yl)phosphonate (trans-11a). Yellowish oil; IR (film, cm^{−1}) ν_{max} : 3085, 2980, 2929, 2782, 1687, 1610, 1469, 1331, 1132, 1098, 1052,

968, 775. $^1\text{H-NMR}$ (600 MHz, CDCl_3): δ = 10.13 (s, 1H, NH), 8.31–8.29 (m, 1H), 7.80–7.78 (m, 1H), 7.71–7.69 (m, 1H), 7.53–7.50 (m, 1H), 5.04 (dd, $^3J_{(\text{H}5-\text{H}4\beta)} = 8.3$ Hz, $^3J_{(\text{H}5-\text{H}4\alpha)} = 6.2$ Hz, 1H, HC5), 4.29–4.20 (m, 4H, $2 \times \text{CH}_2\text{OP}$), 3.28–3.24 (m, 1H, HC3), 3.13 (dddd, $^3J_{(\text{H}4\beta-\text{P})} = 16.9$ Hz, $^2J_{(\text{H}4\beta-\text{H}4\alpha)} = 12.8$ Hz, $^3J_{(\text{H}4\beta-\text{H}3)} = 8.3$ Hz, $^3J_{(\text{H}4\beta-\text{H}5)} = 8.3$ Hz, 1H, $\text{H}_\beta\text{C4}$), 3.05 (s, 3H, CH_3N), 2.96 (dddd, $^2J_{(\text{H}4\alpha-\text{H}4\beta)} = 12.8$ Hz, $^3J_{(\text{H}4\alpha-\text{P})} = 9.9$ Hz, $^3J_{(\text{H}4\alpha-\text{H}3)} = 9.3$ Hz, $^3J_{(\text{H}4\alpha-\text{H}5)} = 6.2$ Hz, 1H, $\text{H}_\alpha\text{C4}$), 1.40 (t, $^3J = 7.1$ Hz, 3H, $\text{CH}_3\text{CH}_2\text{OP}$), 1.38 (t, $^3J = 7.2$ Hz, 3H, $\text{CH}_3\text{CH}_2\text{OP}$). $^{13}\text{C-NMR}$ (151 MHz, CDCl_3): δ = 161.75 (s, C(O)), 153.76, 148.61, 134.82, 127.45, 127.15, 126.60, 121.61, 75.82 (d, $^3J_{(\text{CCCP})} = 8.5$ Hz, C5), 63.76 (d, $^1J_{(\text{CP})} = 170.0$ Hz, C3), 63.36 (d, $^2J_{(\text{COP})} = 6.5$ Hz, CH_2OP), 62.59 (d, $^2J_{(\text{COP})} = 7.3$ Hz, CH_2OP), 46.33 (s, CH_3N), 37.77 (d, $^2J_{(\text{CCCP})} = 1.9$ Hz, C4), 16.53 (d, $^3J_{(\text{CCOP})} = 5.7$ Hz, $\text{CH}_3\text{CH}_2\text{OP}$), 16.46 (d, $^3J_{(\text{CCOP})} = 5.6$ Hz, $\text{CH}_3\text{CH}_2\text{OP}$). $^{31}\text{P-NMR}$ (243 MHz, CDCl_3): δ = 20.64. Anal. Calcd. for $\text{C}_{16}\text{H}_{22}\text{N}_3\text{O}_5\text{P} \times 0.25 \text{H}_2\text{O}$: C, 51.68; H, 6.10; N, 11.30. Found: C, 51.63; H, 6.09; N, 11.32.

Diethyl cis-(2-methyl-5-(4-oxo-3,4-dihydroquinazolin-2-yl)isoxazolidin-3-yl)phosphonate (cis-11a). Data noted below correspond to a 17:83 mixture of *trans-11a* and *cis-11a*. Yellowish oil; IR (film, cm^{-1}) ν_{max} : 3202, 3086, 2980, 2926, 2791, 1688, 1610, 1567, 1469, 1392, 1330, 1231, 1163, 1100, 1024, 973, 776, 573. (signals of *cis-11a* were extracted from the spectra of a 17:83 mixture of *trans-11a* and *cis-11a*); $^1\text{H-NMR}$ (600 MHz, CDCl_3): δ = 10.48 (s, 1H, NH), 8.31–8.29 (m, 1H), 7.77–7.75 (m, 1H), 7.67–7.65 (m, 1H), 7.50–7.47 (m, 1H), 5.10 (dd, $^3J_{(\text{H}5-\text{H}4\alpha)} = 9.1$ Hz, $^3J_{(\text{H}5-\text{H}4\beta)} = 3.9$ Hz, 1H, HC5), 4.27–4.11 (m, 4H, $2 \times \text{CH}_2\text{OP}$), 3.21 (dddd, $^3J_{(\text{H}4\alpha-\text{P})} = 11.2$ Hz, $^2J_{(\text{H}4\beta-\text{H}4\alpha)} = 12.6$ Hz, $^3J_{(\text{H}4\alpha-\text{H}5)} = 9.1$ Hz, $^3J_{(\text{H}4\alpha-\text{H}3)} = 9.0$ Hz, 1H, $\text{H}_\alpha\text{C4}$), 3.10 (ddd, $^3J_{(\text{H}3-\text{H}4\alpha)} = 9.0$ Hz, $^3J_{(\text{H}3-\text{H}4\beta)} = 6.5$ Hz, $^2J_{(\text{H}3-\text{P})} = 3.9$ Hz, 1H, HC3), 3.01 (s, 3H, CH_3N), 2.85 (dddd, $^3J_{(\text{H}4\beta-\text{P})} = 20.0$ Hz, $^2J_{(\text{H}4\alpha-\text{H}4\beta)} = 12.6$ Hz, $^3J_{(\text{H}4\beta-\text{H}3)} = 6.5$ Hz, $^3J_{(\text{H}4\beta-\text{H}5)} = 3.9$ Hz, 1H, $\text{H}_\beta\text{C4}$), 1.31 (t, $^3J = 7.5$ Hz, 3H, $\text{CH}_3\text{CH}_2\text{OP}$), 1.25 (t, $^3J = 6.5$ Hz, 3H, $\text{CH}_3\text{CH}_2\text{OP}$). $^{13}\text{C-NMR}$ (151 MHz, CDCl_3): δ = 161.52 (s, C(O)), 156.11, 148.53, 134.53, 127.14, 126.88, 126.67, 121.83, 75.51 (d, $^3J_{(\text{CCCP})} = 7.3$ Hz, C5), 63.66 (d, $^1J_{(\text{CP})} = 168.5$ Hz, C3), 63.23 (d, $^2J_{(\text{COP})} = 6.6$ Hz, CH_2OP), 63.03 (d, $^2J_{(\text{COP})} = 6.7$ Hz, CH_2OP), 45.62 (d, $^3J_{(\text{CNCP})} = 5.4$ Hz, CH_3N), 37.96 (s, C4), 16.38 (d, $^3J_{(\text{CCOP})} = 5.5$ Hz, $\text{CH}_3\text{CH}_2\text{OP}$), 16.35 (d, $^3J_{(\text{CCOP})} = 5.5$ Hz, $\text{CH}_3\text{CH}_2\text{OP}$). $^{31}\text{P-NMR}$ (243 MHz, CDCl_3): δ = 20.87. Anal. Calcd. for $\text{C}_{16}\text{H}_{22}\text{N}_3\text{O}_5\text{P} \times 0.25 \text{H}_2\text{O}$: C, 51.68; H, 6.10; N, 11.30. Found: C, 51.63; H, 6.05; N, 11.32 (obtained on a 90:10 mixture of *trans-11a* and *cis-11a*).

Diethyl trans-(5-(3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylisoxazolidin-3-yl)phosphonate (trans-11b). Yellowish oil; IR (film, cm^{-1}) ν_{max} : 3065, 3033, 2981, 2915, 2779, 1687, 1620, 1574, 1498, 1455, 1347, 1239, 1104, 1026, 966, 774, 683. $^1\text{H-NMR}$ (600 MHz, CDCl_3): δ = 8.22–8.20 (m, 1H), 7.97–7.95 (m, 1H), 7.84–7.82 (m, 1H), 7.57–7.54 (m, 1H), 7.43–7.41 (m, 1H), 7.38–7.36 (m, 1H), 5.67 (s, 2H, N- CH_2), 5.28 (dd, $^3J_{(\text{H}5-\text{H}4\beta)} = 7.4$ Hz, $^3J_{(\text{H}5-\text{H}4\alpha)} = 6.5$ Hz, 1H, HC5), 4.33–4.20 (m, 4H, $2 \times \text{CH}_2\text{OP}$), 3.45–3.42 (m, 1H, HC3), 3.06 (s, 3H, CH_3N), 3.07–2.97 (m, 2H, $\text{H}_\alpha\text{C4}$, $\text{H}_\beta\text{C4}$), 1.42 (t, $^3J = 7.0$ Hz, 3H, $\text{CH}_3\text{CH}_2\text{OP}$), 1.39 (t, $^3J = 7.1$ Hz, 3H, $\text{CH}_3\text{CH}_2\text{OP}$). $^{13}\text{C-NMR}$ (151 MHz, CDCl_3): δ = 167.04 (s, C(O)), 162.94, 151.27, 136.14, 133.71, 128.59, 128.30, 128.24, 127.86, 127.12, 123.50, 115.60, 80.30 (d, $^3J_{(\text{CCCP})} = 8.6$ Hz, C5), 68.73 (s, CH_2N), 64.44 (d, $^1J_{(\text{CP})} = 168.2$ Hz, C3), 63.25 (d, $^2J_{(\text{COP})} = 6.5$ Hz, CH_2OP), 62.55 (d, $^2J_{(\text{COP})} = 6.9$ Hz, CH_2OP), 46.63 (s, CH_3N), 37.95 (s, C4), 16.56 (d, $^3J_{(\text{CCOP})} = 5.6$ Hz, $\text{CH}_3\text{CH}_2\text{OP}$), 16.51 (d, $^3J_{(\text{CCOP})} = 5.6$ Hz, $\text{CH}_3\text{CH}_2\text{OP}$). $^{31}\text{P-NMR}$ (243 MHz, CDCl_3): δ = 22.19. Anal. Calcd. for $\text{C}_{23}\text{H}_{28}\text{N}_3\text{O}_5\text{P}$: C, 60.39; H, 6.17; N, 9.19. Found: C, 59.99; H, 6.21; N, 9.15.

Diethyl trans-(2-methyl-5-(3-(2-nitrobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl)isoxazolidin-3-yl)-phosphonate (trans-11c). Yellowish oil; IR (film, cm^{-1}) ν_{max} : 3067, 2973, 2918, 1620, 1576, 1526, 1347, 1337, 1264, 1050, 1018, 964, 790, 733, 584, 571. $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ = 8.18–8.07 (m, 2H), 7.93–7.69 (m, 3H), 7.60–7.42 (m, 3H), 6.01 (s, 2H, N- CH_2), 5.15 (dd, $^3J_{(\text{H}5-\text{H}4\beta)} = 7.8$ Hz, $^3J_{(\text{H}5-\text{H}4\alpha)} = 6.1$ Hz, 1H, HC5), 4.29–4.07 (m, 4H, $2 \times \text{CH}_2\text{OP}$), 3.28 (ddd, $^3J_{(\text{H}3-\text{H}4\alpha)} = 10.6$ Hz, $^3J_{(\text{H}3-\text{H}4\beta)} = 8.5$ Hz, $^2J_{(\text{H}3-\text{P})} = 1.2$ Hz, 1H, HC3), 2.93 (s, 3H, CH_3N), 2.99–2.82 (m, 1H, $\text{H}_\beta\text{C4}$), 2.76 (dddd, $^3J_{(\text{H}4\alpha-\text{P})} = 12.5$ Hz, $^2J_{(\text{H}4\alpha-\text{H}4\beta)} = 12.5$ Hz, $^3J_{(\text{H}4\alpha-\text{H}3)} = 10.6$ Hz, $^3J_{(\text{H}4\alpha-\text{H}5)} = 6.1$ Hz, 1H, $\text{H}_\alpha\text{C4}$), 1.33 (t, $^3J = 7.0$ Hz, 3H, $\text{CH}_3\text{CH}_2\text{OP}$), 1.31 (t, $^3J = 7.0$ Hz, 3H, $\text{CH}_3\text{CH}_2\text{OP}$). $^{13}\text{C-NMR}$ (151 MHz, CDCl_3): δ = 166.51 (s, C(O)), 162.99, 151.40, 147.85, 133.98, 133.68, 132.46, 129.10, 128.82, 128.08, 127.44, 125.06, 123.19, 115.30, 80.23 (d, $^3J_{(\text{CCCP})} = 8.4$ Hz, C5), 65.34 (s, N- CH_2), 64.33 (d, $^1J_{(\text{CP})} = 168.4$ Hz, C3), 63.19 (d,

$^2J_{(\text{COP})} = 6.5$ Hz, CH_2OP), 62.44 (d, $^2J_{(\text{COP})} = 7.1$ Hz, CH_2OP), 46.58 (d, $^3J_{(\text{CNCP})} = 3.8$ Hz, CH_3N), 37.98 (s, C4), 16.55 (d, $^3J_{(\text{CCOP})} = 6.4$ Hz, $\text{CH}_3\text{CH}_2\text{OP}$), 16.49 (d, $^3J_{(\text{CCOP})} = 5.7$ Hz, $\text{CH}_3\text{CH}_2\text{OP}$). ^{31}P -NMR (81 MHz, CDCl_3): $\delta = 22.85$. Anal. Calcd. for $\text{C}_{23}\text{H}_{27}\text{N}_4\text{O}_7\text{P} \times 0.25 \text{H}_2\text{O}$: C, 54.49; H, 5.47; N, 11.05. Found: C, 54.42; H, 5.28; N, 10.89.

Diethyl trans-(2-methyl-5-(3-(3-nitrobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl)isoxazolidin-3-yl)-phosphonate (trans-11d). Data noted below correspond to a 92:8 mixture of *trans-11d* and *cis-11d*. A yellowish oil; IR (film, cm^{-1}) ν_{max} : 3070, 2982, 2930, 2910, 1620, 1574, 1531, 1497, 1415, 1298, 1103, 1025, 774, 733, 682. (signals of *trans-11d* were extracted from the spectra of a 92:8 mixture of *trans-11d* and *cis-11d*); ^1H -NMR (600 MHz, CDCl_3): $\delta = 8.46$ – 8.44 (m, 1H), 8.25– 8.22 (m, 2H), 8.00– 7.98 (m, 1H), 7.91– 7.88 (m, 2H), 7.63– 7.60 (m, 2H), 5.78 (s, 2H, N- CH_2), 5.28 (dd, $^3J_{(\text{H5-H4}\beta)} = 6.8$ Hz, $^3J_{(\text{H5-H4}\alpha)} = 6.8$ Hz, 1H, HC5), 4.33– 4.20 (m, 4H, 2 \times CH_2OP), 3.40– 3.38 (m, 1H, HC3), 3.07– 3.00 (m, 1H, $\text{H}_\beta\text{C4}$), 3.05 (s, 3H, CH_3N), 2.98 (dddd, $^3J_{(\text{H4}\alpha\text{-P})} = 12.2$ Hz, $^2J_{(\text{H4}\alpha\text{-H4}\beta)} = 12.2$ Hz, $^3J_{(\text{H4}\alpha\text{-H3})} = 9.8$ Hz, $^3J_{(\text{H4}\alpha\text{-H5})} = 6.8$ Hz, 1H, $\text{H}_\alpha\text{C4}$), 1.42 (t, $^3J = 7.1$ Hz, 3H, $\text{CH}_3\text{CH}_2\text{OP}$), 1.40 (t, $^3J = 6.7$ Hz, 3H, $\text{CH}_3\text{CH}_2\text{OP}$). ^{13}C -NMR (151 MHz, CDCl_3): $\delta = 166.54$ (s, C(O)), 162.63, 151.38, 148.50, 138.29, 134.06, 133.97, 129.65, 128.02, 127.45, 123.25, 123.00, 115.30, 80.14 (d, $^3J_{(\text{CCCP})} = 8.4$ Hz, C5), 67.21 (s, N- CH_2), 64.42 (d, $^1J_{(\text{CP})} = 168.5$ Hz, C3), 63.24 (d, $^2J_{(\text{COP})} = 6.5$ Hz, CH_2OP), 62.44 (d, $^2J_{(\text{COP})} = 7.2$ Hz, CH_2OP), 46.33 (s, CH_3N), 37.84 (s, C4), 16.56 (d, $^3J_{(\text{CCOP})} = 5.6$ Hz, $\text{CH}_3\text{CH}_2\text{OP}$), 16.46 (d, $^3J_{(\text{CCOP})} = 4.2$ Hz, $\text{CH}_3\text{CH}_2\text{OP}$). ^{31}P -NMR (243 MHz, CDCl_3): $\delta = 22.07$. Anal. Calcd. for $\text{C}_{23}\text{H}_{27}\text{N}_4\text{O}_7\text{P}$: C, 54.98; H, 5.42; N, 11.15. Found: C, 54.62; H, 5.24; N, 11.14 (obtained on a 92:8 mixture of *trans-11d* and *cis-11d*).

Diethyl trans-(2-methyl-5-(3-(4-nitrobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl)isoxazolidin-3-yl)-phosphonate (trans-11e). Data noted below correspond to a 90:10 mixture of *trans-11e* and *cis-11e*. A yellowish oil; IR (film, cm^{-1}) ν_{max} : 3073, 2982, 2929, 2781, 1687, 1608, 1523, 1498, 1342, 1106, 968, 851, 739. (signals of *trans-11e* were extracted from the spectra of a 90:10 mixture of *trans-11e* and *cis-11e*); ^1H -NMR (600 MHz, CDCl_3): $\delta = 8.29$ – 8.27 (m, 2H), 8.23– 8.21 (m, 1H), 8.00– 7.98 (m, 1H), 7.89– 7.86 (m, 1H), 7.72– 7.70 (m, 2H), 7.62– 7.60 (m, 1H), 5.77 (s, 2H, N- CH_2), 5.26 (dd, $^3J_{(\text{H5-H4}\beta)} = 6.8$ Hz, $^3J_{(\text{H5-H4}\alpha)} = 6.8$ Hz, 1H, HC5), 4.33– 4.19 (m, 4H, 2 \times CH_2OP), 3.38– 3.35 (m, 1H, HC3), 3.05 (s, 3H, CH_3N), 3.04– 2.91 (m, 2H, $\text{H}_\alpha\text{C4}$, $\text{H}_\beta\text{C4}$), 1.41 (t, $^3J = 7.2$ Hz, 3H, $\text{CH}_3\text{CH}_2\text{OP}$), 1.39 (t, $^3J = 7.2$ Hz, 3H, $\text{CH}_3\text{CH}_2\text{OP}$). ^{13}C -NMR (151 MHz, CDCl_3): $\delta = 166.51$ (s, C(O)), 162.65, 151.35, 147.82, 143.45, 134.04, 128.90, 128.45, 128.07, 127.48, 123.84, 123.19, 115.29, 80.10 (d, $^3J_{(\text{CCCP})} = 8.8$ Hz, C5), 67.18 (s, N- CH_2), 64.42 (d, $^1J_{(\text{CP})} = 168.6$ Hz, C3), 63.25 (d, $^2J_{(\text{COP})} = 5.3$ Hz, CH_2OP), 62.46 (d, $^2J_{(\text{COP})} = 6.9$ Hz, CH_2OP), 46.58 (s, CH_3N), 37.84 (s, C4), 16.55 (d, $^3J_{(\text{CCOP})} = 5.6$ Hz, $\text{CH}_3\text{CH}_2\text{OP}$), 16.50 (d, $^3J_{(\text{CCOP})} = 5.7$ Hz, $\text{CH}_3\text{CH}_2\text{OP}$). ^{31}P -NMR (243 MHz, CDCl_3): $\delta = 22.05$. Anal. Calcd. for $\text{C}_{23}\text{H}_{27}\text{N}_4\text{O}_7\text{P} \times 0.5 \text{H}_2\text{O}$: C, 54.01; H, 5.52; N, 10.95. Found: C, 53.91; H, 5.24; N, 10.95 (obtained on a 90:10 mixture of *trans-11e* and *cis-11e*).

Diethyl trans-(5-(3-(2-fluorobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylisoxazolidin-3-yl)-phosphonate (trans-11f). Data noted below correspond to a 90:10 mixture of *trans-11f* and *cis-11f*. A colorless oil; IR (film, cm^{-1}) ν_{max} : 3067, 2981, 2930, 2909, 1620, 1574, 1498, 1457, 1418, 1346, 1298, 1162, 1101, 1025, 965, 770, 682. (signals of *trans-11f* were extracted from the spectra of a 90:10 mixture of *trans-11f* and *cis-11f*); ^1H -NMR (600 MHz, CDCl_3): $\delta = 8.17$ – 8.15 (m, 1H), 7.95– 7.93 (m, 1H), 7.83– 7.80 (m, 1H), 7.58– 7.52 (m, 2H), 7.36– 7.32 (m, 1H), 7.17– 7.15 (m, 1H), 7.13– 7.10 (m, 1H), 5.73 (AB, $^2J_{\text{AB}} = 12.6$ Hz, 1H, N- CH_{2b}), 5.70 (AB, $^2J_{\text{AB}} = 12.6$ Hz, 1H, N- CH_{2a}), 5.26 (dd, $^3J_{(\text{H5-H4}\beta)} = 7.3$ Hz, $^3J_{(\text{H5-H4}\alpha)} = 6.7$ Hz, 1H, HC5), 4.32– 4.18 (m, 4H, 2 \times CH_2OP), 3.43– 3.40 (m, 1H, HC3), 3.04 (s, 3H, CH_3N), 3.03– 2.93 (m, 2H, $\text{H}_\alpha\text{C4}$, $\text{H}_\beta\text{C4}$), 1.40 (t, $^3J = 7.0$ Hz, 3H, $\text{CH}_3\text{CH}_2\text{OP}$), 1.38 (t, $^3J = 7.1$ Hz, 3H, $\text{CH}_3\text{CH}_2\text{OP}$). ^{13}C -NMR (151.0 MHz, CDCl_3): $\delta = 166.86$ (s, C(O)), 162.84, 161.08 (d, $^1J_{(\text{CF})} = 248.6$ Hz, C2'), 151.19, 133.76, 130.60 (d, $^3J_{(\text{CCCCF})} = 3.4$ Hz, C4'), 130.26 (d, $^3J_{(\text{CCCCF})} = 8.6$ Hz, C6'), 127.85, 127.17, 124.17 (d, $^4J_{(\text{CCCCF})} = 3.3$ Hz, C5'), 123.45, 123.31 (d, $^2J_{(\text{CCF})} = 14.3$ Hz, C3'), 115.54 (d, $^2J_{(\text{CCF})} = 21.4$ Hz, C1'), 115.49, 80.27 (dd, $^3J_{(\text{CCCP})} = 8.7$ Hz, C5), 64.41 (d, $^1J_{(\text{CP})} = 168.3$ Hz, C3), 63.23 (d, $^2J_{(\text{COP})} = 6.3$ Hz, CH_2OP), 62.60 (d, $^3J = 4.3$ Hz, CH_2N), 62.39 (d, $^2J_{(\text{COP})} = 6.8$ Hz, CH_2OP), 46.61 (s, CH_3N), 37.94 (s, C4), 16.56 (d, $^3J_{(\text{CCOP})} = 5.6$ Hz, $\text{CH}_3\text{CH}_2\text{OP}$), 16.50 (d, $^3J_{(\text{CCOP})} = 5.6$ Hz, $\text{CH}_3\text{CH}_2\text{OP}$). ^{31}P -NMR (243 MHz, CDCl_3): $\delta = 22.16$. Anal. Calcd. for

$C_{23}H_{27}FN_3O_5P \times 0.5 H_2O$: C, 57.02; H, 5.83; N, 8.67. Found: C, 57.30; H, 5.58; N, 8.62 (obtained on a 90:10 mixture of *trans*-**11f** and *cis*-**11f**).

Diethyl trans-(5-(3-(3-fluorobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylisoxazolidin-3-yl)-phosphonate (trans-11g). Colorless oil; IR (film, cm^{-1}) ν_{max} : 3066, 2982, 2909, 1620, 1575, 1497, 1452, 1416, 1343, 1299, 1163, 1104, 966, 775, 682. 1H -NMR (600 MHz, $CDCl_3$): δ = 8.22–8.20 (m, 1H), 7.98–7.96 (m, 1H), 7.86–7.84 (m, 1H), 7.59–7.57 (m, 1H), 7.40–7.37 (m, 1H), 7.31–7.28 (m, 2H), 7.08–7.06 (m, 1H), 5.66 (s, 2H, N-CH₂), 5.27 (dd, $^3J_{(H5-H4\beta)}$ = 7.4 Hz, $^3J_{(H5-H4\alpha)}$ = 6.7 Hz, 1H, HC5), 4.33–4.21 (m, 4H, 2 \times CH₂OP), 3.42–3.40 (m, 1H, HC3), 3.05 (s, 3H, CH₃N), 3.04–2.94 (m, 2H, H _{α} C4, H _{β} C4) 1.42 (t, 3J = 7.1 Hz, 3H, CH₃CH₂OP), 1.39 (t, 3J = 7.0 Hz, 3H, CH₃CH₂OP). ^{13}C -NMR (151 MHz, $CDCl_3$): δ = 166.80 (s, C(O)), 162.92 (d, $^1J_{(CF)}$ = 246.6 Hz, C3'), 162.80, 151.25, 138.65 (d, $^3J_{(CCCCF)}$ = 7.6 Hz, C5'), 133.84, 130.17 (d, J = 8.7 Hz, C1'), 127.94, 127.27, 123.60 (d, $^4J_{(CCCCF)}$ = 2.6 Hz, C6'), 123.39, 115.47, 115.18 (d, $^2J_{(CCF)}$ = 21.0 Hz, C4'), 115.00 (d, $^2J_{(CCF)}$ = 22.0 Hz, C2'), 80.22 (dd, $^3J_{(CCCCP)}$ = 7.9 Hz, C5), 67.80 (d, 3J = 1.6 Hz, CH₂N), 64.43 (d, $^1J_{(CP)}$ = 168.3 Hz, C3), 63.26 (d, $^2J_{(COP)}$ = 6.7 Hz, CH₂OP), 62.41 (d, $^2J_{(COP)}$ = 6.4 Hz, CH₂OP), 46.59 (s, CH₃N), 37.92 (s, C4), 16.56 (d, $^3J_{(CCOP)}$ = 5.6 Hz, CH₃CH₂OP), 16.50 (d, $^3J_{(CCOP)}$ = 5.6 Hz, CH₃CH₂OP). ^{31}P -NMR (243 MHz, $CDCl_3$): δ = 22.14. Anal. Calcd. for $C_{23}H_{27}FN_3O_5P \times 0.5 H_2O$: C, 57.02; H, 5.83; N, 8.67. Found: C, 57.30; H, 5.66; N, 8.74.

Diethyl trans-(5-(3-(4-fluorobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylisoxazolidin-3-yl)-phosphonate (trans-11h). Colorless oil; IR (film, cm^{-1}) ν_{max} : 3069, 2982, 2930, 2910, 1620, 1574, 1512, 1498, 1226, 1104, 966, 823, 774, 683. 1H -NMR (600 MHz, $CDCl_3$): δ = 8.17–8.15 (m, 1H), 7.96–7.94 (m, 1H), 7.84–7.81 (m, 1H), 7.56–7.51 (m, 3H), 7.11–7.08 (m, 2H), 5.62 (s, 2H, N-CH₂), 5.27 (dd, $^3J_{(H5-H4\beta)}$ = 6.7 Hz, $^3J_{(H5-H4\alpha)}$ = 6.7 Hz, 1H, HC5), 4.32–4.20 (m, 4H, 2 \times CH₂OP), 3.43–3.40 (m, 1H, HC3), 3.07–2.99 (m, 1H, H _{β} C4), 3.06 (s, 3H, CH₃N), 2.99 (dddd, $^3J_{(H4\alpha-P)}$ = 12.5 Hz, $^2J_{(H4\alpha-H4\beta)}$ = 12.5 Hz, $^3J_{(H4\alpha-H3)}$ = 10.3 Hz, $^3J_{(H4\alpha-H5)}$ = 6.7 Hz, 1H, H _{α} C4), 1.41 (t, 3J = 7.1 Hz, 3H, CH₃CH₂OP), 1.39 (t, 3J = 6.4 Hz, 3H, CH₃CH₂OP). ^{13}C -NMR (151 MHz, $CDCl_3$): δ = 166.90 (s, C(O)), 162.84, 162.73 (d, $^1J_{(CF)}$ = 246.9 Hz, C4'), 151.21, 133.76, 131.93 (d, $^4J_{(CCCCF)}$ = 3.2 Hz, C1'), 130.28 (d, $^3J_{(CCCCF)}$ = 8.0 Hz, C2', C6'), 127.89, 127.18, 123.41, 115.53 (d, $^2J_{(CCF)}$ = 21.4 Hz, C3', C5'), 115.52, 80.23 (d, $^3J_{(CCP)}$ = 8.1 Hz, C5), 68.02 (s, N-CH₂), 64.45 (d, $^1J_{(CP)}$ = 168.1 Hz, C3), 63.25 (d, $^2J_{(COP)}$ = 6.4 Hz, CH₂OP), 62.39 (d, $^2J_{(COP)}$ = 6.9 Hz, CH₂OP), 46.62 (s, CH₃N), 37.96 (s, C4), 16.56 (d, $^3J_{(CCOP)}$ = 5.6 Hz, CH₃CH₂OP), 16.50 (d, $^3J_{(CCOP)}$ = 5.5 Hz, CH₃CH₂OP). ^{31}P -NMR (243 MHz, $CDCl_3$): δ = 22.13. Anal. Calcd. for $C_{23}H_{27}FN_3O_5P$: C, 58.10; H, 5.72; N, 8.84. Found: C, 57.74; H, 5.70; N, 8.77.

Diethyl trans-(5-(3-(2,4-difluorobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylisoxazolidin-3-yl)-phosphonate (trans-11i). Data noted below correspond to a 92:8 mixture of *trans*-**11i** and *cis*-**11i**. A colorless oil; IR (film, cm^{-1}) ν_{max} : 3068, 2982, 2930, 2910, 1621, 1574, 1498, 1416, 1162, 1102, 1025, 961, 773, 682. (signals of *trans*-**11i** were extracted from the spectra of a 92:8 mixture of *trans*-**11i** and *cis*-**11i**); 1H -NMR (600 MHz, $CDCl_3$): δ = 8.18–8.16 (m, 1H), 7.98–7.96 (m, 1H), 7.86–7.84 (m, 1H), 7.62–7.56 (m, 2H), 6.95–6.89 (m, 2H), 5.71 (AB, $^2J_{AB}$ = 12.4 Hz, 1H, N-CH_{2b}), 5.71 (AB, $^2J_{AB}$ = 12.4 Hz, 1H, N-CH_{2a}), 5.29 (dd, $^3J_{(H5-H4\beta)}$ = 6.6 Hz, $^3J_{(H5-H4\alpha)}$ = 6.2 Hz, 1H, HC5), 4.34–4.22 (m, 4H, 2 \times CH₂OP), 3.44–3.41 (m, 1H, C3), 3.07 (s, 3H, CH₃-N), 3.04–3.02 (m, 1H, H _{β} C4), 3.01 (dddd, $^3J_{(H4\alpha-P)}$ = 12.4 Hz, $^2J_{(H4\alpha-H4\beta)}$ = 12.4 Hz, $^3J_{(H4\alpha-H3)}$ = 10.1 Hz, $^3J_{(H4\alpha-H5)}$ = 6.2 Hz, 1H, H _{α} C4), 1.43 (t, 3J = 7.1 Hz, 3H, CH₃CH₂OP), 1.41 (t, 3J = 7.0 Hz, 3H, CH₃CH₂OP). ^{13}C -NMR (151 MHz, $CDCl_3$): δ = 165.94 (s, C(O)), 163.05 (dd, $^1J_{(CF)}$ = 265.3 Hz, $^3J_{(CCCCF)}$ = 12.1 Hz, C2'), 162.71, 161.44 (dd, $^1J_{(CF)}$ = 266.1 Hz, $^3J_{(CCCCF)}$ = 14.4 Hz, C4'), 151.19, 133.76, 131.87 (dd, $^3J_{(CCCCF)}$ = 9.9 Hz, $^3J_{(CCCCF)}$ = 5.5 Hz, C6'), 127.85, 127.18, 123.33, 119.34 (dd, $^2J_{(CCF)}$ = 14.5 Hz, $^4J_{(CCCCF)}$ = 3.3 Hz, C1'), 115.38, 111.35 (dd, $^2J_{(CCF)}$ = 21.0 Hz, $^4J_{(CCCCF)}$ = 3.3 Hz, C5'), 104.02 (dd, $^2J_{(CCF)}$ = 25.3 Hz, $^2J_{(CCF)}$ = 25.3 Hz, C3'), 80.20 (dd, $^3J_{(CCCCP)}$ = 8.7 Hz, $^3J_{(CCCCF)}$ = 2.3 Hz, C5), 64.41 (d, $^1J_{(CP)}$ = 168.2 Hz, C3), 63.19 (d, $^2J_{(COP)}$ = 6.1 Hz, CH₂OP), 62.35 (d, $^2J_{(COP)}$ = 7.3 Hz, CH₂OP), 62.04 (d, $^3J_{(CCCCF)}$ = 3.2 Hz, CH₂N), 46.45 (d, $^3J_{(CNCP)}$ = 2.6 Hz, CH₃N), 37.89 (d, $^2J_{(CCP)}$ = 1.7 Hz, C4), 16.52 (d, $^3J_{(CCOP)}$ = 5.5 Hz, CH₃CH₂OP), 16.45 (d, $^3J_{(CCOP)}$ = 5.5 Hz, CH₃CH₂OP). ^{31}P -NMR (243 MHz, $CDCl_3$): δ = 22.13. Anal. Calcd. for $C_{23}H_{26}F_2N_3O_5P \times 0.5 H_2O$: C, 54.98; H, 5.42; N, 8.36. Found: C, 55.08; H, 5.14; N, 8.26 (obtained on a 92:8 mixture of *trans*-**11i** and *cis*-**11i**).

Diethyl trans-(2-methyl-5-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)isoxazolidin-3-yl)phosphonate (trans-11j). Colorless oil; IR (film, cm^{-1}) ν_{max} : 2983, 2955, 2924, 2854, 1679, 1601, 1474, 1435, 1340, 1299, 1241, 1053, 1022, 945, 781, 695, 653, 600, 559. $^1\text{H-NMR}$ (600 MHz, CDCl_3): δ = 8.28–8.25 (m, 1H), 7.75–7.72 (m, 1H), 7.68–7.66 (m, 1H), 7.50–7.47 (m, 1H), 5.18 (dd, $^3J_{(\text{H5-H4}\beta)} = 7.7 \text{ Hz}$, $^3J_{(\text{H5-H4}\alpha)} = 5.6 \text{ Hz}$, 1H, HC5), 4.30–4.22 (m, 4H, $2 \times \text{CH}_2\text{OP}$), 3.75 (dddd, $^3J_{(\text{H4}\alpha\text{-P})} = 14.0 \text{ Hz}$, $^2J_{(\text{H4}\alpha\text{-H4}\beta)} = 12.7 \text{ Hz}$, $^3J_{(\text{H4}\alpha\text{-H3})} = 9.1 \text{ Hz}$, $^3J_{(\text{H4}\alpha\text{-H5})} = 5.6 \text{ Hz}$, 1H, $\text{H}_\beta\text{C4}$), 3.74 (s, 3H, CH_3N), 3.37 (ddd, $^3J_{(\text{H3-H4}\alpha)} = 9.1 \text{ Hz}$, $^3J_{(\text{H3-H4}\beta)} = 7.7 \text{ Hz}$, $^2J_{(\text{H3-P})} = 2.7 \text{ Hz}$, 1H, HC3), 2.79 (dddd, $^3J_{(\text{H4}\beta\text{-P})} = 15.4 \text{ Hz}$, $^2J_{(\text{H4}\beta\text{-H4}\alpha)} = 12.7 \text{ Hz}$, $^3J_{(\text{H4}\beta\text{-H3})} = 7.7 \text{ Hz}$, $^3J_{(\text{H4}\beta\text{-H5})} = 7.7 \text{ Hz}$, 1H, $\text{H}_\beta\text{C4}$), 1.40 (t, $^3J = 7.1 \text{ Hz}$, 3H, $\text{CH}_3\text{CH}_2\text{OP}$), 1.39 (t, $^3J = 7.1 \text{ Hz}$, 3H, $\text{CH}_3\text{CH}_2\text{OP}$). $^{13}\text{C-NMR}$ (151 MHz, CDCl_3): δ = 162.50 (s, C(O)), 152.24, 146.52, 134.08, 127.62, 127.41, 126.79, 120.98, 76.37 (d, $^3J_{(\text{CCCP})} = 7.8 \text{ Hz}$, C5), 64.38 (d, $^1J_{(\text{CP})} = 170.6 \text{ Hz}$, C3), 63.02 (d, $^2J_{(\text{COP})} = 6.6 \text{ Hz}$, CH_2OP), 62.70 (d, $^2J_{(\text{COP})} = 6.9 \text{ Hz}$, CH_2OP), 47.21 (d, $^3J_{(\text{CNCP})} = 6.3 \text{ Hz}$, CH_3N), 34.41 (s, C4), 30.77 (s, CH_3N) 16.56 (d, $^3J_{(\text{CCOP})} = 5.0 \text{ Hz}$, $\text{CH}_3\text{CH}_2\text{OP}$), 16.53 (d, $^3J_{(\text{CCOP})} = 4.9 \text{ Hz}$, $\text{CH}_3\text{CH}_2\text{OP}$). $^{31}\text{P-NMR}$ (243 MHz, CDCl_3): δ = 22.09. Anal. Calcd. for $\text{C}_{17}\text{H}_{24}\text{N}_3\text{O}_5\text{P} \times \text{H}_2\text{O}$: C, 51.13; H, 6.56; N, 10.52. Found: C, 51.23; H, 6.17; N, 10.49.

Diethyl trans-(5-(3-ethyl-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylisoxazolidin-3-yl)phosphonate (trans-11k). Data noted below correspond to a 94:6 mixture of *trans-11k* and *cis-11k*. Yellowish oil; IR (film, cm^{-1}) ν_{max} : 3068, 2981, 2930, 2870, 1620, 1574, 1501, 1424, 1382, 1340, 1240, 1164, 1105, 1053, 1023, 967, 774, 684, 581. (signals of *trans-11k* were extracted from the spectra of a 94:6 mixture of *trans-11k* and *cis-11k*); $^1\text{H-NMR}$ (600 MHz, CDCl_3): δ = 8.19–8.17 (m, 1H), 7.96–7.94 (m, 1H), 7.84–7.82 (m, 1H), 7.58–7.55 (m, 1H), 5.26 (dd, $^3J_{(\text{H5-H4}\beta)} = 7.4 \text{ Hz}$, $^3J_{(\text{H5-H4}\alpha)} = 6.4 \text{ Hz}$, 1H, HC5), 4.69 (q, $^3J = 7.1 \text{ Hz}$, 2H, CH_3CH_2), 4.34–4.21 (m, 4H, $2 \times \text{CH}_2\text{OP}$), 3.49–3.46 (m, 1H, HC3), 3.08 (s, 3H, CH_3N), 3.10–2.96 (m, 2H, $\text{H}_\alpha\text{C4}$, $\text{H}_\beta\text{C4}$), 1.55 (t, $^3J = 7.1 \text{ Hz}$, 3H, CH_3CH_2), 1.42 (t, $^3J = 7.0 \text{ Hz}$, 3H, $\text{CH}_3\text{CH}_2\text{OP}$), 1.39 (t, $^3J = 7.1 \text{ Hz}$, 3H, $\text{CH}_3\text{CH}_2\text{OP}$). $^{13}\text{C-NMR}$ (151 MHz, CDCl_3): δ = 167.25 (s, C(O)), 163.16, 151.03, 133.51, 127.77, 126.92, 123.44, 115.60, 80.36 (d, $^3J_{(\text{CCCP})} = 8.3 \text{ Hz}$, C5), 64.38 (d, $^1J_{(\text{CP})} = 168.2 \text{ Hz}$, C3), 63.23 (d, $^2J_{(\text{COP})} = 6.4 \text{ Hz}$, CH_2OP), 62.36 (d, $^2J_{(\text{COP})} = 6.7 \text{ Hz}$, CH_2OP), 47.21 (d, $^3J_{(\text{CNCP})} = 6.3 \text{ Hz}$, CH_3N), 34.41 (s, C4), 29.64 (s, CH_3CH_2) 16.53 (d, $^3J_{(\text{CCOP})} = 5.7 \text{ Hz}$, $\text{CH}_3\text{CH}_2\text{OP}$), 16.47 (d, $^3J_{(\text{CCOP})} = 5.8 \text{ Hz}$, $\text{CH}_3\text{CH}_2\text{OP}$), 14.29 (s, CH_3CH_2). $^{31}\text{P-NMR}$ (243 MHz, CDCl_3): δ = 22.23. Anal. Calcd. for $\text{C}_{18}\text{H}_{26}\text{N}_3\text{O}_5\text{P}$: C, 54.68; H, 6.63; N, 10.63. Found: C, 54.93; H, 6.51; N, 10.21 (obtained on a 94:6 mixture of *trans-11k* and *cis-11k*).

3.5. Antiviral Activity Assays

The compounds were evaluated against different herpesviruses, including herpes simplex virus type 1 (HSV-1) strain KOS, thymidine kinase-deficient (TK^-) HSV-1 KOS strain resistant to ACV (ACV^r), herpes simplex virus type 2 (HSV-2) strain G, varicella-zoster virus (VZV) strain Oka, TK^- VZV strain 07-1, human cytomegalovirus (HCMV) strains AD-169 and Davis as well as feline herpes virus (FHV), the poxvirus vaccinia virus (Lederle strain), para-influenza-3 virus, reovirus-1, Sindbis virus, Coxsackie virus B4, Punta Toro virus, respiratory syncytial virus (RSV), feline coronavirus (FIPV) and influenza A virus subtypes H1N1 (A/PR/8), H3N2 (A/HK/7/87) and influenza B virus (B/HK/5/72) and human immune deficiency virus (5HVV-1 and HIV-2). The antiviral assays, other than HIV, were based on inhibition of virus-induced cytopathicity or plaque formation in human embryonic lung (HEL) fibroblasts, African green monkey kidney cells (Vero), human epithelial cervix carcinoma cells (HeLa), Crandell-Rees feline kidney cells (CRFK), or Madin Darby canine kidney cells (MDCK). Confluent cell cultures in microtiter 96-well plates were inoculated with 100 CCID₅₀ of virus (1 CCID₅₀ being the virus dose to infect 50% of the cell cultures) or with 20 plaque forming units (PFU) and the cell cultures were incubated in the presence of varying concentrations of the test compounds. Viral cytopathicity or plaque formation (VZV) was recorded as soon as it reached completion in the control virus-infected cell cultures that were not treated with the test compounds. Antiviral activity was expressed as the EC₅₀ or compound concentration required to reduce virus-induced cytopathicity or viral plaque formation by 50%. Cytotoxicity of the test compounds was expressed as the minimum cytotoxic concentration (MCC) or the compound concentration that caused a microscopically detectable alteration of cell morphology.

3.6. Cytostatic Activity against Immortalized Cell Lines

Murine leukemia (L1210), human T-lymphocyte (CEM), human cervix carcinoma (HeLa) and immortalized human dermal microvascular endothelial cells (HMEC-1) were suspended at 300,000–500,000 cells/mL of culture medium, and 100 μ L of a cell suspension was added to 100 μ L of an appropriate dilution of the test compounds in 200 μ L-wells of 96-well microtiter plates. After incubation at 37 °C for two (L1210), three (CEM) or four (HeLa) days, the cell number was determined using a Coulter counter. The IC₅₀ was defined as the compound concentration required to inhibit cell proliferation by 50%.

4. Conclusions

A series of isoxazolidine-containing quinazolinones *trans*-**11** and *cis*-**11** have been synthesised from *N*-methyl-*C*-diethoxyphosphorylnitron (12) and the respective N3-substituted 2-vinyl-quinazolin-ones **13** via the 1,3-dipolar cycloaddition. The obtained isoxazolidine phosphonates *trans*-**11** or the respective mixtures of *trans*-**11**/*cis*-**11** were evaluated against a variety of DNA and RNA viruses. Among all tested compounds, isoxazolidines *trans*-**11f**/*cis*-**11f** (90:10), *trans*-**11h** and *trans*-**11i**/*cis*-**11i** were slightly active toward TK⁺VZV strain (EC₅₀ = 6.84, 15.29 and 9.44 μ M) without exhibiting cytotoxicity toward uninfected cells at concentration up to 100 μ M. On the other hand, phosphonates *trans*-**11b**/*cis*-**11b** (90:10), *trans*-**11c**, *trans*-**11e**/*cis*-**11e** (90:10) and *trans*-**11g** showed weak antiviral properties against cytomegalovirus (EC₅₀ = 27–45 μ M).

Compounds equipped with benzyl substituents at N3 in the quinazolinone skeleton exhibited some antiproliferative activity toward the tested immortalized cells (IC₅₀ = 21–102 μ M), while analogues lacking substituent or having alkyl group at N3 were inactive. These results encourage us to continue the search for more active compounds with special focus on modification the quinazoline-4-one unit especially at N3.

Supplementary Materials: Supplementary materials can be accessed at: <http://www.mdpi.com/1420-3049/21/7/959/s1>.

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Author Contributions: Research group from Medical University of Lodz (D.G.P. and M.G.-D.) conceived the research project, participated in all steps of the research, interpreted the results, discussed the experimental data and prepared the manuscript. Research group from KU Leuven (G.A., D.S. and R.S.) conducted the biological assays and provided the experimental procedures and results. All authors read, commented and approved the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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Sample Availability: Samples of the compounds are not available from the authors.



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